Neuroimaging Predictors of Treatment Response in Posttraumatic Stress Disorder

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Abstract

Although there are several treatment options available for posttraumatic stress disorder (PTSD) none of them have a 100% success rate. Approximately half of the individuals who complete CBT will continue to show symptoms of the disorder, and little progress has been made in discovering biological predictors of treatment response in the disorder. Finding such biological predictors would be useful in helping select a treatment that is best for individual patients, thereby increasing the number of individuals who no longer exhibit PTSD symptoms. Using functional magnetic resonance imaging (fMRI), we measured brain activation in 14 participants who passively viewed emotional facial expressions before receiving eight sessions of prolonged exposure therapy (PE). Response to treatment was measured using clinician-administered scales – the Short PTSD Rated Interview (SPRINT) and the Clinical Global Improvement (CGI-I) scale. We conducted correlations in order to assess the relationship between participants' pre-treatment brain activation and their improvement scores on each of these scales. Overall, our results showed that greater pre-treatment activation in the rostral anterior cingulate cortex (rACC) and lower pre-treatment activation in the amygdala led to better responses to treatment. These results suggest that measuring brain activation may be a useful tool to use in the future to predict treatment response.

Keywords: PTSD, predictors, treatment, functional magnetic resonance imaging, amygdala, medial prefrontal cortex, anterior cingulate cortex

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Neuroimaging Predictors of Treatment Response in Posttraumatic Stress Disorder

Posttraumatic stress disorder (PTSD) is a debilitating disorder that effects approximately 7.8% of the general population (Kessler, Sonnega, & Bromet, 1995; 2005). An individual can be diagnosed with the disorder if they have experienced a traumatic event involving threatened death, physical injury, or witnessing the death or injury of others. Additionally, the diagnostic criteria for PTSD include three main symptom clusters: re-experiencing the trauma, avoiding cues that are associated with the trauma, and hyper-arousal (DSM-IV-TR[1], American Psychiatric Association, 2000). In order to be diagnosed with PTSD, a patient must show at least one symptom from the re-experiencing cluster, at least three symptoms from the avoidance cluster and at least two symptoms from the hyper-arousal cluster for at least one month (DSM-IV-TR, American Psychiatric Association, 2000).

Several treatment options are available for PTSD which include treatments that fall under the category of cognitive behavioral therapy (CBT). Currently, 30-50% of PTSD patients who receive treatment such as CBT will still show symptoms after completion (Bradley et al., 2005). Unfortunately, this contributes to the continued distress these patients face. For example, some patients may spend months, even years, cycling though therapies before finding the one that actually provides some relief. Moreover, PTSD contributes to an increased risk of medical problems such as heart disease, hypertension, hyperlipidemia, and obesity (McFarlane, 2010). Additionally, PTSD affects more than the individual with the disorder. On average, PTSD patients have around four days of work impairment per month, which translates into an annual productivity loss of close to $3 billion in the U.S. (Kessler, 2000).

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[1] DSM-IV-TR criteria was discussed since all participant were screened using these criteria for this study.

Thus, given that PTSD is a serious problem for both the individual suffering from the disorder and society as a whole, it would be advantageous for clinicians to identify pre-treatment measures that could help predict treatment response for patients.

Neurocircuitry of PTSD

Over the past two decades, there has been an increase in research conducted on the potential biological mechanisms of PTSD. In order to understand these biological mechanisms, neuroimaging techniques have been used to examine brain regions that are affected in the disorder. Studies thus far have found abnormalities in the limbic and prefrontal structures (e.g., Francati et al., 2007; Karl et al., 2006; Hughes & Shin, 2011). Specifically, these areas include the amygdala and the medial prefrontal cortex (mPFC). The amygdala is an important brain structure in the disorder given its role in the acquisition and expression of conditioned fear, i.e., learning that a previously neutral cue (e.g., road-side trash) is associated with an aversive event (e.g., explosion of a bomb covered in trash). Additionally, the mPFC, which includes regions of the rostral anterior cingulate cortex (rACC) and medial frontal gyrus, is responsible for inhibiting the amygdala when appropriate. In other words, the mPFC is responsible for extinguishing the association made between the neutral cue and the aversive event. Both animal and human studies have provided evidence for this claim. For example, Quirk et al. (2000) showed that rats with lesions to their ventral mPFC were able to extinguish conditioned fear, however a day later their fear memory recovered. These results suggest that the ventral mPFC is responsible for recalling that a stimulus that used to predict danger no longer does (Quirk et al., 2000). Furthermore, Phelps et al. (2004) found that the subgenual anterior cingulate, a region in the mPFC, was most activated during tests of extinction in humans, adding further evidence of the role of the mPFC in recalling the extinguished association (Phelps et al., 2004).

In PTSD, the amygdala has been shown to be hyperactive, while the rACC is hypoactive, in a variety of tasks (Rauch et al., 1998; Rauch et al., 2006; VanElzakker, Staples, & Shin, 2013). Thus, it appears that the prefrontal cortical structures fail to inhibit the amygdala in PTSD, making it hard to successfully extinguish conditioned fear in the disorder. While neuroimaging techniques have helped elucidate the pathophysiology of PTSD, they may also have the potential to predict response to treatment.

Predictor Studies

Clinical studies. Some of the earliest predictor studies focused on using personality traits to predict how well a PTSD patient would respond to treatment. For example, individuals with higher levels of alexithymia (i.e., the inability to verbalize ones' feelings and thoughts) before participating in CBT showed a poorer response to treatment (Kosten, et al., 1992; Brady, Warnock-Parkes, Barker, & Ehlers, 2015). Furthermore, Taylor et al. (2001) examined treatment response in PTSD patients of road traffic collisions. The authors found that those who exhibited more pre-treatment numbing symptoms, greater anger about their trauma, lower levels of global functioning, and those taking psychotropic medication had a poorer response to CBT (Taylor et al., 2001).

Cognitive constructs have also been used to determine how successful a treatment might be for an individual. A study conducted by Ehlers and colleagues (1998) found that the feeling of mental defeat after suffering a trauma, along with the feeling of alienation and permanent change resulted in a poorer response to exposure therapy (Ehlers et al., 1998). Furthermore, a study conducted by Nijdam and colleagues (2015) found that PTSD patients who had poorer verbal memory before receiving treatment responded worse to trauma-focused psychotherapy (Nijdam, Vries, Gersons, & Olff, 2015). More recently, Böttche et al. (2016) discovered that PTSD

patients who had higher ratings on both self-perception of controllability and self-understanding responded better to internet-based CBT (Böttche, Kuwert, Pietrzak, & Knaevelsrud, 2016).

Additionally, many studies have assessed whether demographic and clinical characteristics (such as sex, age, age of PTSD symptom onset, and number of traumas experienced) predict how well a PTSD participant will respond to treatment. For example, lower pre-treatment levels of avoidance symptoms and less severe PTSD symptomatology predicted a better response to brofaromine, while age, duration of symptoms, type of trauma and autonomic arousal symptoms were not predictive factors (Connor et al., 2001). Women who experienced childhood trauma and who did not sustain physical injury during an assault in adulthood showed a better response to treatment (Hembree, Street, Riggs, & Foa, 2004). Additionally, being female and having a shorter duration of treatment were also related to a better response to treatment (Karatzias et al., 2007; Tarrier et al., 2000). Lastly, older individuals and higher educational levels predicted better outcomes after both cognitive processing therapy and prolonged exposure (PE) therapy in patients with PTSD (Rizvi, Vogt, & Resick 2009).

Biological studies. To date, clinical and demographic characteristics have been rather poor predictors of treatment response (Cloitre et al., 2016). Because of this, studies have been conducted to find biological measures that could be potentially helpful in guiding clinician-based decision making. Such measures include the serotonin transporter (5-HTTPLR; Bryant et al., 2010), brain-derived neurotrophic factor (BDNF; Felmingham et al., 2013), cortisol (Yehuda et al., 2014; Rauch et al., 2015), and neuroimaging techniques. Here, we will focus on neuroimaging studies.

Neuroimaging studies.

Structural imaging studies. Only recently have studies examined structural neuroimaging predictors of treatment response in PTSD. In one such study conducted by Bryant and colleagues (2008), all participants underwent structural magnetic resonance imaging (MRI) procedures before receiving 8 weekly sessions of CBT and were then reassessed for a PTSD diagnosis. Their results showed larger pre-treatment rACC volumes predicted a better response to CBT (Bryant et al., 2008). Additionally, Nardo et al. (2010) used voxel-based morphology (VBM) to compare gray matter densities between responders of eye-movement desensitization (EDMR) to non-responders. The authors found that greater pre-treatment concentrations of grey matter in the posterior cingulate, parahippocampal gyrus, insula, and the right amygdala in individuals with PTSD predicted a better response to EMDR therapy (Nardo et al., 2010). Lastly, a more recent study conducted by Rubin and colleagues (2016) used structural MRI to examine baseline hippocampal volumes in individuals with PTSD. The authors found individuals who exhibited greater baseline hippocampal volume responded better to PE (Rubin et al., 2016).

Functional imaging studies. Other studies have been conducted to determine whether functional neuroimaging techniques, such as functional magnetic resonance imaging (fMRI), can help predict treatment response. Bryant and colleagues (2008) had participants view images of fearful and neutral facial expressions before receiving 8 weekly treatment session of exposure-based therapy. Their results showed that PTSD patients who exhibited greater pre-treatment bilateral amygdala and right ventral ACC during the presentation of fearful stimuli had a poorer response to CBT (Bryant et al., 2008). Additionally, Aupperle et al. (2013) found that greater pre-treatment posterior cingulate and dorsal/rostral ACC activation during an anticipation task and less dorsal ACC activation during the presentation of negative-positive affective images was

related to better treatment response to cognitive trauma therapy in PTSD patients who experienced intimate partner violence (Aupperle et al., 2013). Furthermore, Cisler et al. (2015) found greater pre-treatment bilateral amygdala activation while viewing both threat and neutral facial expressions predicted a poorer response to trauma-focused CBT treatment response among assaulted adolescent girls with PTSD. However, the authors also found that greater pre-treatment amygdala signal change when viewing fearful vs. neutral facial expressions was associated with a better response to treatment (Cisler et al., 2015).

Falconer, Allen, and Felmingham (2013) examined whether measurement of the inhibitory control systems of the brain, focusing on the dorsal striatal and frontal cognitive control network, would help in predicting treatment response in PTSD. PTSD patients completed a Go/No-Go paradigm that assessed inhibitory performance during fMRI scanning before receiving 8 weekly sessions of CBT. Their results showed that PTSD patients who exhibited greater activation in their left dorsal striatal and frontal cognitive control network exhibited a greater response to CBT while greater activation in the right ventrolateral prefrontal cortex was associated with a poorer response to CBT (Falconer, Allen, & Felmingham, 2013).

Additionally, van Rooij and colleagues (2016) had veterans with PTSD complete a trauma-unrelated emotional processing task while in a fMRI scanner. During the task they were asked to rate each picture shown as either neutral, negative, or positive. Participants who displayed greater pre-treatment dorsal anterior cingulate cortex (dACC), insula, and amygdala activation towards trauma-unrelated negative stimuli had persistent symptoms after receiving treatment (van Rooij et al., 2016).

Lastly, a more recent study conducted by Fonzo et al. (2017) found PTSD participants with greater pre-treatment activation in the dACC, anterior insula, dorsolateral prefrontal cortex

(DLPFC), and lesser amygdala activation when processing fearful (vs. neutral) facial expressions showed a better response to treatment. Additionally, they found PTSD patients with greater pre-treatment vmPFC/ventral striatal activation during the implicit regulation of emotional conflict (i.e., naming fearful and happy facial expression with congruent or incongruent emotional words) showed an even better response to treatment (Fonzo et al., 2017).

Current Study

As outlined above, previous research has examined multiple clinical, demographic, and biological predictors of treatment response in PTSD. Our study hopes to build upon these findings by using trauma-unrelated emotional stimuli such as fearful facial expressions as a predictor of response to PE. Facial expressions play an important role in our every day lives as they help in predicting potential threat. Previous neuroimaging studies have shown emotional facial expressions elicit both amygdala and prefrontal cortex activation in both healthy and PTSD populations (Shin et al., 2005; Williams et al., 2006; Kemp et al., 2007; Dickie et al., 2008, El Khoury-Malhame et al., 2011; Brohawn et al., 2010; Mahabir et al., 2015).

Based on previous evidence, we hypothesized that greater pre-treatment activation in mPFC regions, including the rACC, will be associated with better response to PE treatment. Secondly, we hypothesized that lesser pre-treatment activation in the amygdala will be associated with a better response to PE.

Methods

Participants

Participants were 22 (12 female) treatment–seeking PTSD subjects. Eight participants dropped out before the study's completion and their initial scores were excluded from analysis. Thus, the final sample size consisted of 14 (8 female) PTSD patients who were without a history

of head injury, neurological disorders, or other major medical conditions. None of the female participants were pregnant at the time of the study, as indicated by an early detection urine pregnancy test taken before fMRI scanning procedures. The Partners Healthcare System (Boston, MA) Institutional Review Board approved this study. Written informed consent was obtained prior to participation in the study.

Demographics and Psychometrics

Subjects were screened and offered study inclusion if all entry criteria were met. Before beginning imaging procedures, patients completed an evaluation, which included: (1) Mini-International Neuropsychiatric Interview (MINI; Sheehan et al., 1998) to diagnose Axis I psychiatric disorders; (2) the Short PTSD Rating Interview (SPRINT; Connor & Davidson, 2001) an eight-item clinician administered scale that measures the severity of the core symptoms of PTSD; and (3) the Clinical Global Impression Severity Scale (CGI-S; Guy, 1976), a one-item scale that asks the clinician to rate overall illness severity (see Table 1 and 2 for participants' demographic and clinical characteristics). During the last treatment session, the Clinical Global Impression Improvement Scale (CGI-I; Guy, 1976), a one-item scale designed to measure the participants' overall improvement of symptoms, was administered. The SPRINT was also administered during the last treatment session in order to obtain a post-treatment score. Baseline post-treatment SPRINT scores were subtracted from participant's pre-treatment SPRINT scores in order to create a SPRINT change score. Additionally, in order to control for baseline SPRINT scores, this difference was then divided by pre-treatment SPRINT scores and multiplied by 100 in order to obtain a SPRINT percent improvement score. Both will be used for correlational analyses. Regression analyses were also performed using participants' demographic information and treatment response variables.

Task Procedures

In the scanner, each participant viewed gray scale images of 6 happy, 6 neutral, and 6 fearful facial expressions that have already been well-validated in previous studies (Ekman & Friesen, 1976). Each type of facial expression was posed by 3 men and 3 women. The presentation of each face lasted for 200-milliseconds, with a 300-millisecond interstimulus interval, in a pseudorandom order such that facial expressions of a single individual were not presented twice in a row. Happy, neutral, and fearful faces were presented in separate alternating blocks (e.g., +N F H F H F H N+), and the order of emotional block was counterbalanced across subjects. The stimuli were displayed using MacStim 3.0 software. After exiting the scanner, participants rated the facial expressions on 7-point scales of valence and arousal. Specifically, valence was measured on a scale from -3 to 3, where -3 represents negative and 3 represents positive valence. Arousal was measured on a scale from 0 to 6, where 0 represents low arousal and 6 represents high arousal. Participants' average rating on valence and arousal for each facial expression was correlated with SPRINT percent improvement scores in order to determine whether they predicted treatment response.

FMRI Procedures

Scans were collected from a Symphony/Sonata 1.5-Tesla whole body high-speed imaging device equipped for echo planar imaging (Siemens Medical Systems, Iselin, NJ) with a 12-axis gradient head coil. We restricted head movement by using expandable foam cushions. Field homogeneity was optimized by conducting shimming procedures after acquiring an automated scout image. Shimming procedures and high-resolution 3D magnetization-prepared rapid acquisition gradient echo (mprage) sequence were gathered in a sagittal plane, with scan parameters as follows: repetition time/echo time/flip angle, 2.73 seconds/3.39

milliseconds/12.50°. T2-weighted sequence functional images were gathered in the coronal plane, with scan parameters as follows: repetition time/echo time/flip angle, 2.8 seconds/40 milliseconds/90°. We gathered fMRI data in 24 coronal slices angled perpendicular to the anterior commissure-posterior commissure line with slice thickness at 7 millimeters, skip 1millimeter; voxel size, 3.1x3.1x7 millimeter.

Treatment Procedures

After scanning was complete, participants underwent 8 weekly 90-minute treatment sessions of PE with a doctoral-level clinician. PE was developed after the emotional processing theory (Foa & Kozak, 1986), that describes fear as a structure which includes the fear stimuli and fear response. An abnormal fear response consists of an individual becoming fearful of a stimulus that becomes associated with the fear, leading to an overgeneralization of fear responding to otherwise safe situations. Thus, in order to correct this abnormal fear structure, during therapy the individual needs to activate the fear structure (e.g., discuss the trauma), and then integrate new information about the fear structure that confirms the individual is now safe. In order to do this, PE involves three components. The first is *in vivo* exposure where the patient and clinician list all stimuli that the patient avoids, allowing the clinician to slowly have the patient expose himself to the reminders and learn that the feared stimuli are not harmful. The second component involves imaginal exposure to the memory of the most distressing traumatic event the patient experienced. Specifically, clinicians will have the patient discuss their traumas out loud while their session is recorded. The clinician is likely to then have the patient listen to their recordings as homework. Both these components were designed to have the patient be exposed to their trauma reminders for a period of time long enough to allow emotional and

physiological responses to decline. The last component involves reviewing what was learning during both *in vivo* and imaginal exposures.

Data Analysis

Functional MRI data analysis. Image preprocessing and statistical analyses were performed using SPM2, a statistical parametric mapping software package to conduct whole-brain voxel-wise analyses as well as region of interest (ROI) analyses (http://www.fil.ion.ucl.ac.uk/spm/;Wellcome Department of Imaging Neuroscience, London, UK). Functional images of each participant were co-registered to their high-resolution structural MRI image (mprage), smoothed (4mm), and spatially normalized with standard stereotactic space (Montreal Neurological Institute, MNI). Hypotheses were tested as contrasts where linear compounds of the model parameters are evaluated using *t* statistics, which were then transformed into *z* scores.

For whole-brain voxelwise analyses, we computed voxelwise fearful vs. happy contrasts within each subject and correlated these contrasts with symptomatic improvement. We chose to focus on the fearful vs. happy contrast in particular because this is the contrast used by previous studies to demonstrate differences in activation between individuals with PTSD compared to trauma-exposed non-PTSD controls (Rauch et al., 2000; Shin et al., 2005). In order to prevent habituation or sensitization effects, all analyses were conducted within the first functional run of the task.

For ROI analyses, we computed the voxelwise fearful vs. happy contrast within each subject and ran a one-group t-test to assess amygdala and mPFC activation across all of our participants. In order to determine whether signal activation in these brain regions were significantly related to treatment response, we (1) defined a functional region of interest (sphere

radius of 4mm) around activations in the amygdala and mPFC, (rACC and medial frontal gyrus), during run 1 in all subjects; (2) extracted signal values per condition per subject from each region; (3) calculated the fearful vs. happy signal change value per subject; and (4) determined whether those change values were correlated with SPRINT percent improvement, SPRINT change scores, and CGI-I scores using correlational analyses.

Statistics

The statistical parametric group maps that were created from the voxelwise analyses were examined for activations in our *a priori* regions of interest. Based on previous work, the significant threshold for the strong, directional hypotheses was $p<.001$ (z score, ≥ 3.09) for activations in these regions (Hariri et al, 2002; Phan et al, 2003; Shin et al, 2005). We chose to use a constant significance threshold since the procedure of correcting p values based on region size is biased toward finding significance in small structures. For regions that had no a priori prediction, we used a more conservative constant significance threshold of $p<.00001$ (z score, $\geq$ 4.27; Shin et al, 2005).

Results

The average pre-treatment SPRINT score was 21.5 ($SD = 5.65$), corresponding to markedly-severe PTSD. The average SPRINT percent improvement across participants was 46% ($SD = 39.16$). The average initial CGI-S score was 4.8 ($SD = 0.77$), corresponding to markedly-severe PTSD, and the average CGI-I score was 2.5 ($SD = 1.16$), corresponding to much improved symptom severity across treatment.

Valence/Arousal Ratings

Pearson correlation coefficients assessing the relationship between the participants' ratings of valence and arousal of the neutral facial expression (see Table 3 for mean and standard

deviation of ratings) and SPRINT percent improvement scores were not significant: valence r(12) = .265, *p* =.361 and arousal, r(12) = -.021, *p* = .943. Non-significant results also were found between valence and arousal ratings of the happy facial expression and SPRINT percent improvement scores: valence r(12) = .394, *p* = .164 and arousal, r(12) = -.014, *p* = .961. Lastly non-significant results were found between valence and arousal ratings of the fearful facial expression and SPRINT percent improvement score: valence, r(12) = .189, *p* = .517 and arousal, r(12) = .288, *p* = .318.

Demographic and Trauma Variables

Separate simultaneous multivariate regressions were used to assess participants' demographic (e.g., age, education, gender) and trauma (e.g., time since trauma) variables with each of our measures of treatment response. Contrary to previous findings, (Karatzias et al., 2007) demographic and trauma variables were found to not significantly predict SPRINT percent improvement scores ($F(4, 9) = .398$, $p = .805$), SPRINT change scores ($F(4, 9) = .509$, $p = .731$), or CGI-I scores ($F(4, 9) = .186$, $p = .940$).

FMRI Data

Whole-brain voxelwise correlational analyses.

SPRINT percent improvement. Voxelwise correlational analyses were used to determine the relationship between pre-treatment brain activation and SPRINT percent improvement scores. In line with our hypotheses, strong positive correlations were found between three different areas in the rACC (MNI coordinates, 6, 42, -4; MNI coordinates, -8, 42, -4; MNI coordinates, 14, 40, 2) and SPRINT percent improvement scores, r(12) = .705, *p* = .005, r(12) = .886, *p* = .000, and r(12) = .776, *p* = .001, respectively (see Figure 1, 2, and 3) indicating that individuals with PTSD who had greater pre-treatment rACC activation showed a better response

to PE. Furthermore, strong negative correlations were found between pre-treatment amygdala (MNI coordinates, 26, -8, -14) and SPRINT percent improvement scores, $r(12) = -.754$, $p = .002$ (see Figure 4) indicating that individuals with PTSD who had greater pre-treatment amygdala activation had a poorer response to PE. Lastly, contrary to our hypotheses a strong negative correlation was found between pre-treatment rACC (MNI coordinates, 6, 46, 4) activation and SPRINT percent improvement, $r(12) = -.636$, $p = .014$ (see Figure 5).

Moderation analyses. Furthermore, given the whole-brain voxelwise findings above of greater pre-treatment mPFC activation and lesser pre-treatment amygdala activation leading to a better response to treatment as measured by SPRINT percent improvement scores, exploratory analyses were conducted to better understand the relationship between these activations. Specifically, we sought to determine if pre-treatment rACC (MNI coordinates, 6, 42, -4; MNI coordinates, -8, 42, -4; MNI coordinates, 14, 40, 2) activations changed the magnitude of the relationship between pre-treatment amygdala (MNI coordinates, 26, -8, -14) activation and SPRINT percent improvement. Multivariate regressions with interactions were computed by adding special Macros to SPSS to test moderation effects (Hayes, 2017). Our results fell short of statistical significance when examining the interaction between pre-treatment rACC (MNI coordinates, 6, 42, -4) and pre-treatment amygdala activation, $R^2 = .0106$, $F(3, 10) = .4022$, $p = .5402$. Our results also fell short of statistical significance when examining the interaction between pre-treatment rACC (MNI coordinates, -8, 42, -4) and pre-treatment amygdala activation, $R^2 = .0131$, $F(3, 10) = .8154$, $p = .3878$. Finally, our results fell short of statistical significance when examining the interaction between pre-treatment rACC (MNI coordinates, 14, 40, 2) and pre-treatment amygdala activation, $R^2 = .0019$, $F(3, 10) = .0900$, $p = .7703$. These non-significant interactions indicate that regardless of the amount of pre-treatment rACC

activation present, the relationship between pre-treatment amygdala activation and treatment outcome stays the same. Thus, it may not be the combination of activation that contributes to treatment response, but the independent relationship between these regions of activation and response.

Multivariate regression. Separate simultaneous multivariate regressions were calculated to predict SPRINT percent improvement scores. The first simultaneous regression included demographic variables, time since trauma, and voxelwise brain activations (rACC MNI coordinates, 6, 42, -4; Amygdala MNI coordinates 26, -8, -14) as predictors of SPRINT percent improvement and was nonsignificant $F(6, 7) = 2.424$, $p = .136$, with an R^2 of .822. For this model, one variable was statistically significant in predicting SPRINT percent improvement (see Table 4 for standardized coefficients and significance values for each predictor variable). The second simultaneous regression included demographic variables, time since trauma, and voxelwise brain activations (rACC MNI coordinates, -8, 42, -4; Amygdala MNI coordinates 26, -8, -14) as predictors and was significant $F(6, 7) = 7.606$, $p = .009$, with an R^2 of .931. For this model, one variable was statistically significant in predicting SPRINT percent improvement (see Table 5 for standardized coefficients and significance values for each predictor variable). Lastly, a third simultaneous regression using demographic variables, time since trauma, and voxelwise brain activations (rACC MNI coordinates, 14, 40, 2; Amygdala MNI coordinates 26, -8, -14) as predictors was nonsignificant, $F(6, 7) = 2.801$, $p = .102$, with an R^2 of .840. For this model, one variable was statistically significant in predicting SPRINT percent improvement (see Table 6 for standardized coefficients and significance values for each predictor variable). From these regression analyses it appears that our variables are predicting a majority of the variance in SPRINT percent improvement scores, driven by voxelwise rACC activations.

SPRINT change. Voxelwise correlations between pre-treatment brain activation and SPRINT change scores mirrored that of SPRINT percent improvement results, with strong positive correlations between the rACC (MNI coordinates: -8, 38, -4; MNI coordinates: 6, 42, -4) and SPRINT change scores, $r(12) = .902$, $p = .000$, and $r(12) = .724$, $p = .003$, respectively. Additionally, a strong positive correlation was found between the dorsal rostral ACC (drACC; MNI coordinates, 6, 34, 18) and SPRINT change scores, $r(12) = .787$, $p = .001$ Lastly, a strong positive correlation was found between the DLPFC (MNI coordinates, 48, 38, 16) and SPRINT change scores, $r(12) = .818$, $p = .000$.

CGI-improvement. There were no significant whole-brain voxelwise activations correlated with CGI-I scores.

Region of interest correlational analyses. The one sample t-test conducted using the voxelwise fearful vs. happy contrasts for all subjects revealed significant activations in the mPFC, but no significant activations in the amygdala. ROI's were made in the rACC (MNI coordinates, 0, 36, 6; $z = 3.32$, $p = .000$) and dACC (MNI coordinates, -6, -2, 42; $z = 4.07$, $p = .000$). Pearson correlations were conducted between each ROI and SPRINT percent improvement scores, but they were not statistically significant, $r(12) = .162$, $p = .580$ and $r(12) = .121$, $p = .681$, respectively. Correlations were also conducted between each ROI and SPRINT change scores, but were also not statistically significant, $r(12) = .126$, $p = .668$ and $r(12) = .202$, $p = .488$, respectively. Lastly, correlations between each ROI and participants CGI-I scores were non-significant $r(12) = .111$, $p = .706$ and $r(12) = .072$, $p = .806$, respectively.

Discussion

The current study sought to determine if pre-treatment brain responses collected during the presentation of emotional facial expression cues can be used to help predict symptomatic

change with PE. Our results showed that greater pre-treatment activation in multiple regions of the mPFC and lesser pre-treatment activation in the amygdala predicted a better response to PE (although contrary to our hypotheses, one area of the rACC predicted a poorer response to treatment).

These findings are consistent with those of previous studies. Bryant and colleagues (2008) showed that individuals with PTSD who had greater pre-treatment bilateral amygdala activation during fearful face processing had a poorer response to CBT. Furthermore, a recent study by Fonzo and colleagues (2017) using emotional facial expressions, found that less pretreatment amygdala and greater DLPFC and dACC activation lead to a better response to treatment (Fonzo et al., 2017). Our study provides converging evidence for the above results and builds upon these findings by using multiple regression with an interaction to better understand the relationship between our variables. Furthermore, while a majority of the other studies chose to use CBT, we focused on PE because it is currently one of the most used treatment option for PTSD (Rauch, Eftekhari, & Ruzek, 2012).

Our finding of excessive pre-treatment amygdala activation predicting a poorer response to treatment is consistent with previous findings. Studies of both animal models and humans have shown the amygdala plays an active role in mediating fear responses, as well as fear conditioning and extinction learning (Davis, 1992; LeDoux, 1993; Phelps et al., 2004). In PTSD studies have shown the amygdala to be hyperresponsive (Rauch et al., 1996, 2000; Shin et al., 1997, 2004, 2005; Liberzon et al, 1999; Semple et al., 2000; Pissota et al., 2002; Hendler et al., 2003; Driessen et al, 2004; Protopopescu et al., 2005; Chung et al., 2006; Vermetten et al., 2007; Morey et al., 2008; Handwerger-Brohawn, et al., 2010; Fonzo et al., 2010; St. Jacques et al., 2011; Garrett et al., 2012; Stevens et al., 2013; Whalley et al., 2009). This hyperresponsivity

contributes not only to symptoms of the disorder, but may also affect treatment response. For example, in order for PE to be successful in treating PTSD a patient needs to activate their traumatic memory and reappraise that they are now in a safe context allowing patients to learn that some associations that were made during the time of the trauma are now erroneous and not generalizable to their current situations (Foa & Meadows, 1997). Our results showed that greater pre-treatment amygdala activation may have been detrimental during treatment making it harder for our participants to reprocess relevant information, such as safety associations (Rauch and Foa, 2006).

Our results of greater pre-treatment mPFC predicting a better response to treatment is also consistent with previous research findings. The mPFC plays a crucial role in mediating the amygdala's response to fearful stimuli. As a whole, the mPFC acts as an inhibitor of the amygdala when individuals begin to form new associations, such as learning that they are no longer in the presence of danger even when presented with trauma-related stimuli. Many studies conducted on the integrity of the mPFC in PTSD have shown decreased responsivity in the rACC and other structures associated with the mPFC using many tasks (Shin et al., 2001; Hull, 2002; Lanius et al., 2001, 2002, 2003; Bremner et al., 1999a, 2003; Lindaur et al., 2004; Britton et al., 2005; Williams et al., 2006; Hou et al., 2007). Therefore, it may be that that participants in our study who showed greater pre-treatment activation in the mPFC were more successful in regulating fear responses during PE, effectively reducing PTSD symptoms. Based on these findings, the mPFC may be a good predictor of treatment response since the mPFC plays such an important role in inhibiting the amygdala, regulating fear responses, and recalling extinction learning.

Furthermore, previous studies have suggested the hyperactivity of the amygdala in individuals with PTSD may be attributed to a failure of mPFC regions to exert control over the amygdala (Shin et al., 2006; Kim et al., 2008; Simmons et al., 2011). To determine the relationship between the amygdala and rACC in predicting symptomatic improvement, multiple regression models with interaction terms were found to be statistically nonsignificant. This suggests that it may not be the lack of control of the amygdala by the mPFC that is contributing to the poorer response to treatment, but these two brain regions could potentially be modulating symptomatic improvement independently of one another. Additionally, this could also suggest there are other areas of the ACC that we did not measure that could be moderating the amygdala's relationship with treatment outcome. However, our low sample size might have also contributed to the nonsignificant findings.

Limitations and Future Directions

Our study has many limitations. First, our sample size is small, limiting the statistical power of this study. Adding more participants is a future step that needs to be taken in order to ensure the results we see are stable and generalizable to the larger population of treatment-seeking PTSD patients. Furthermore, we used only PE as a treatment option and lacked a control group. Future studies should examine other therapies such as cognitive processing therapy (CPT) or even medications in order to determine the predictive capacity of neural responses to those treatments. The underlying neurological mechanisms that predict each treatment could potentially be different. Additionally, a waitlisted control group could be added in the future in order to ensure the conclusions drawn from the correlations conducted are caused by treatment response and not just by spontaneous changes over time. Furthermore, in order to better understand the relationships between pre-treatment activation and treatment response, functional

connectivity analyses should be undertaken. Finally, while we used only the first run to examine brain activation, future studies should explore amygdala habituation across runs. Measuring how fast the amygdala habituates across runs may be another tool used to predict treatment response.

In conclusion, our study provides initial evidence that fMRI activation in the amygdala and the mPFC may be suitable predictors for PE. Based on our results, we speculate that patients who presumably had superior inhibition of fear response before treatment (as measured by greater pre-treatment rACC activation) while viewing threat-related stimuli showed the most success to PE. While patients who presumably had inferior inhibition of the fear response to threat-related stimuli (as measured by an increase in amygdala activation) may have benefitted less from PE. However, we must be cautious when making claims with this data since there was a low number of participants that completed the study and the lack of a direct measure of fear inhibition.

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Table 1.

Clinical Characteristics for All Participants (*N = 14)*

Gender	Trauma	Duration (years)	Co-morbidity	Medications
F	Unknown	3	MDD	Klonopin
M	Hold-up	14	MDD	None
F	MVA	4	None	None
F	MVA	1	MDD, PD	Neurontin
M	Combat	1	None	None
M	Combat	30	MDD, PD, GAD	Zoloft, Wellbutrin
F	MVA	4	MDD, SP, PD	None
F	Abuse	20	MDD, SP, PD	Klonopin, Wellbutrin, Amitriptyline, Neurontin
F	IPA	2	MDD	None
M	MVA	.85	PD	None
F	IPA/Combat	19	PD	None
M	Combat	5	GAD	None
M	Abuse	45	GAD, SAD, PD, MDD	Zestrill, Effexor, Klonopin, Trazodone
F	Abuse	31	Dysthymia	Setraline

Note. PTSD = posttraumatic stress disorder; MVA = motor vehicle accident; IPA = intimate partner violence; MDD = major depressive disorder; PD = panic disorder; SP = specific phobia; GAD = generalized anxiety disorder; SAD = social anxiety disorder.

Table 2.

Participant's Psychometric and Demographic Information (N = 14)

	Mean (SD)
Age (years)	46.21 (11.16)
Education (years)	16 (2.77)
Time since trauma (years)	12.66 (14.46)
SPRINT baseline score	21.5 (5.65)
CGI-S score	4.8 (0.77)

Note. The above table represents the means and standard deviations for demographic and psychometric information collected. SD = standard deviation; SPRINT = short PTSD rating interview; CGI-S = clinical global impression improvement scale.

Table 3.

Means and Standard Deviations of Each Rating (Valence, Arousal) for Each Type of Face (Neutral, Fearful, Happy; N = 14)

	Mean (SD)	
Face Type	**Valence**	**Arousal**
Neutral	-0.79 (1.53)	2.33 (3.55)
Fearful	-2.48 (2.77)	4.55 (5.99)
Happy	2.62 (2.71)	4.18 (4.37)

Note. The above table represents the means and standard deviations for each rating: valence and arousal and each type of emotional facial expression presented: neutral, fearful, and happy between all our participants. SD = standard deviation.

Table 4.

Simultaneous Regression Analyses with Demographic Variables and Rostral Anterior Cingulate Cortex (6, 42, -4) and Amygdala (26, -8, -14) Activation Predicting SPRINT Percent Improvement Scores (N = 14)

Predictor	Beta	t	p
Age (years)	.019	.065	.950
Education (years)	.197	.820	.440
Time since trauma (years)	-.131	-.423	.685
Gender	-.061	-.265	.799
rACC (6, 42, -4)	.946	3.356	.012**
Amygdala (26, -8, -14)	.515	1.844	.108

Note. The above table illustrates the standardized coefficients, t-static, and *p* values for each predictor variable. SD = standard deviation; SPRINT = short PTSD rating interview; rACC = rostral anterior cingulate cortex. Gender was represented as two dummy variables with 0 male serving as the reference group. **denotes significance at .05 level.

Table 5.

Simultaneous Regression Analyses with Demographic Variables and Rostral Anterior Cingulate Cortex (-8, 42, -4) and Amygdala (26, -8, -14) Activation Predicting SPRINT Percent Improvement Scores (N = 14)

Predictor	Beta	t	p
Age (years)	.372	1.746	.124
Education (years)	.005	.033	.975
Time since trauma (years)	-.378	-1.812	.113
Gender	-.124	-.840	.429
rACC (-8, 42, -4)	1.090	6.133	.000**
Amygdala (26, -8, -14)	.130	.835	.431

Note. The above table illustrates the standardized coefficients, t-static, and *p* values for each predictor variable. SD = standard deviation; SPRINT = short PTSD rating interview; rACC = rostral anterior cingulate cortex. Gender was represented as two dummy variables with 0 male serving as the reference group. **denotes significance at .05 level.

Table 6.

Simultaneous Regression Analyses with Demographic Variables and Rostral Anterior Cingulate Cortex (14, 40, 2) and Amygdala (26, -8, -14) Activation Predicting SPRINT Percent Improvement Scores (N = 14)

Predictor	Beta	t	p
Age (years)	-.132	-.504	.630
Education (years)	-.094	-.424	.685
Time since trauma (years)	-.161	-.546	.602
Gender	.047	.216	.836
rACC (14, 40, 2)	.821	3.630	.008**
Amygdala (26, -8, -14)	-.057	-.246	.813

Note. The above table illustrates the standardized coefficients, t-static, and *p* values for each predictor variable. SD = standard deviation; SPRINT = short PTSD rating interview; rACC = rostral anterior cingulate cortex. Gender was represented as two dummy variables with 0 male serving as the reference group. **denotes significance at .05 level.

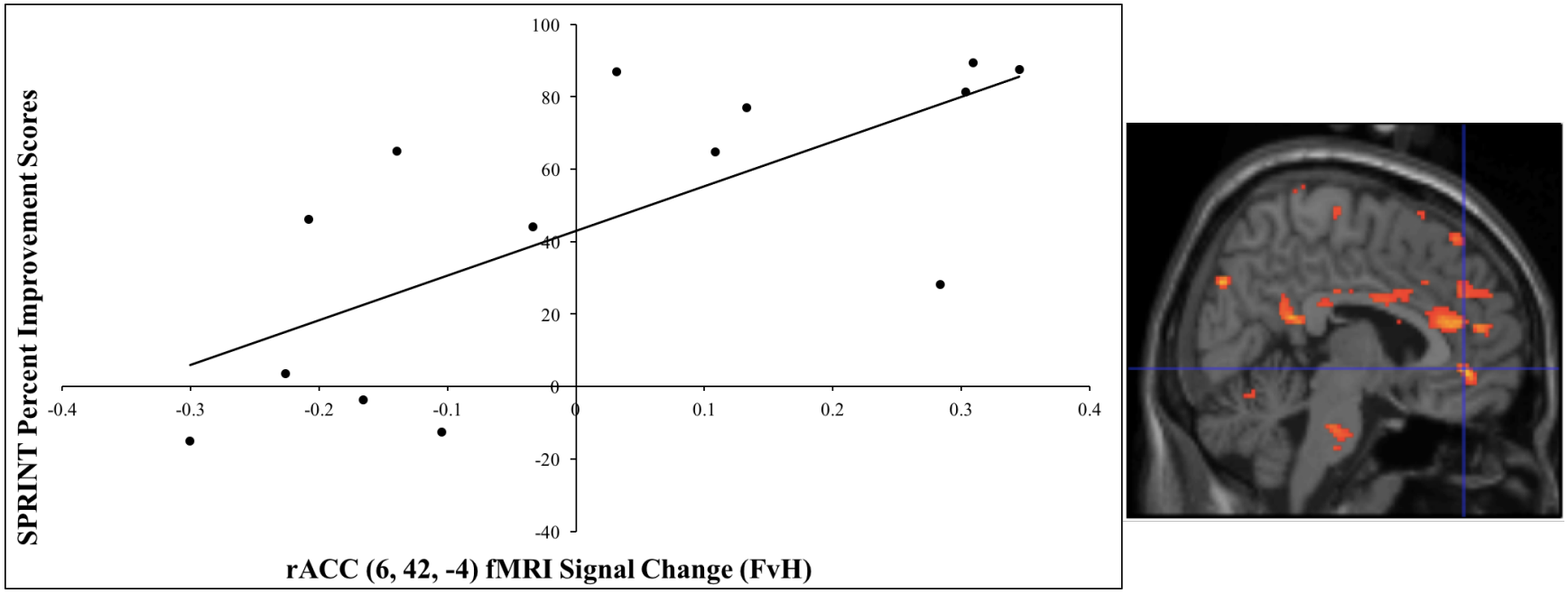

Figure 1. Correlation between pre-treatment activation seen in the rostral anterior cingulate cortex (rACC; MNI coordinates, 6, 42, -4; $z = 3.49$; $p = .000$) during the viewing of fearful versus happy (FvH) facial expressions and symptom severity improvement as measured by the Short Posttraumatic Stress Disorder (PTSD) Rated Interview (SPRINT) percent improvement scores.

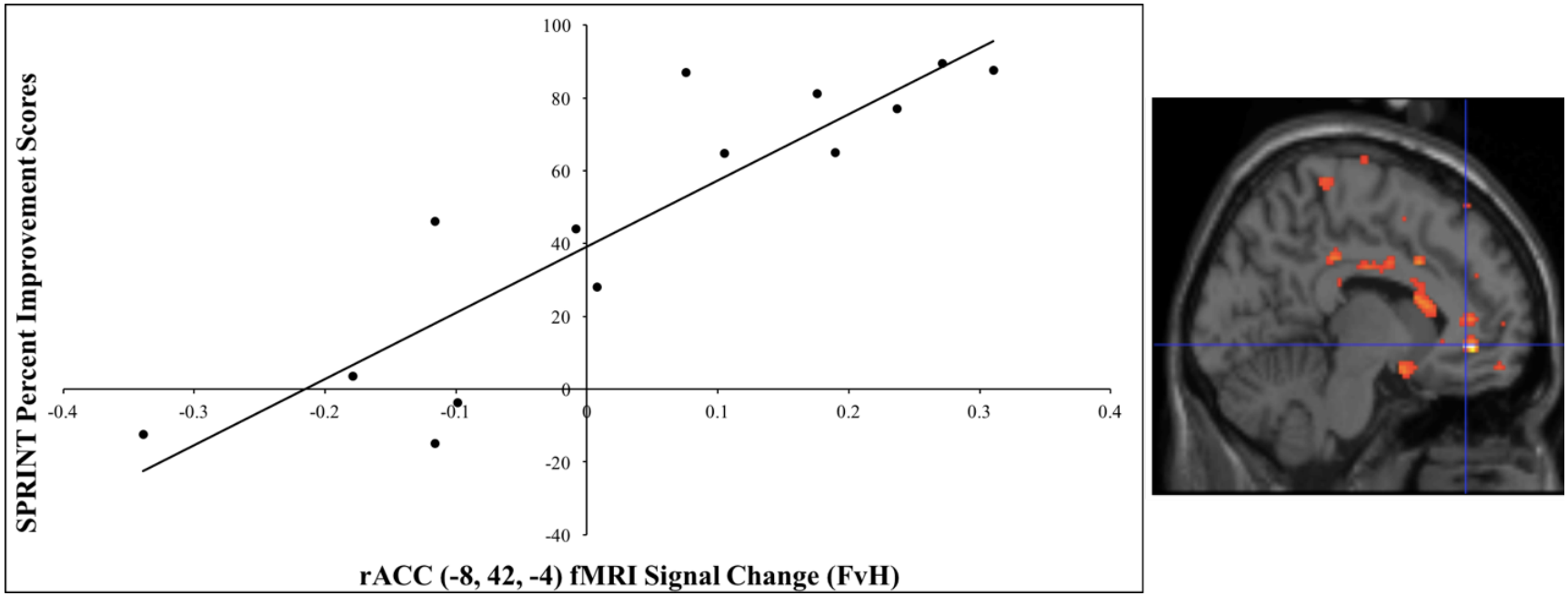

Figure 2. Correlation between pre-treatment activation seen in the rostral anterior cingulate cortex (rACC; MNI coordinates, -8, 42, -4; $z = 4.50$, $p = .000$) during the viewing of fearful versus happy (FvH) facial expressions and symptom severity improvement as measured by the Short Posttraumatic Stress Disorder (PTSD) Rated Interview (SPRINT) percent improvement scores.

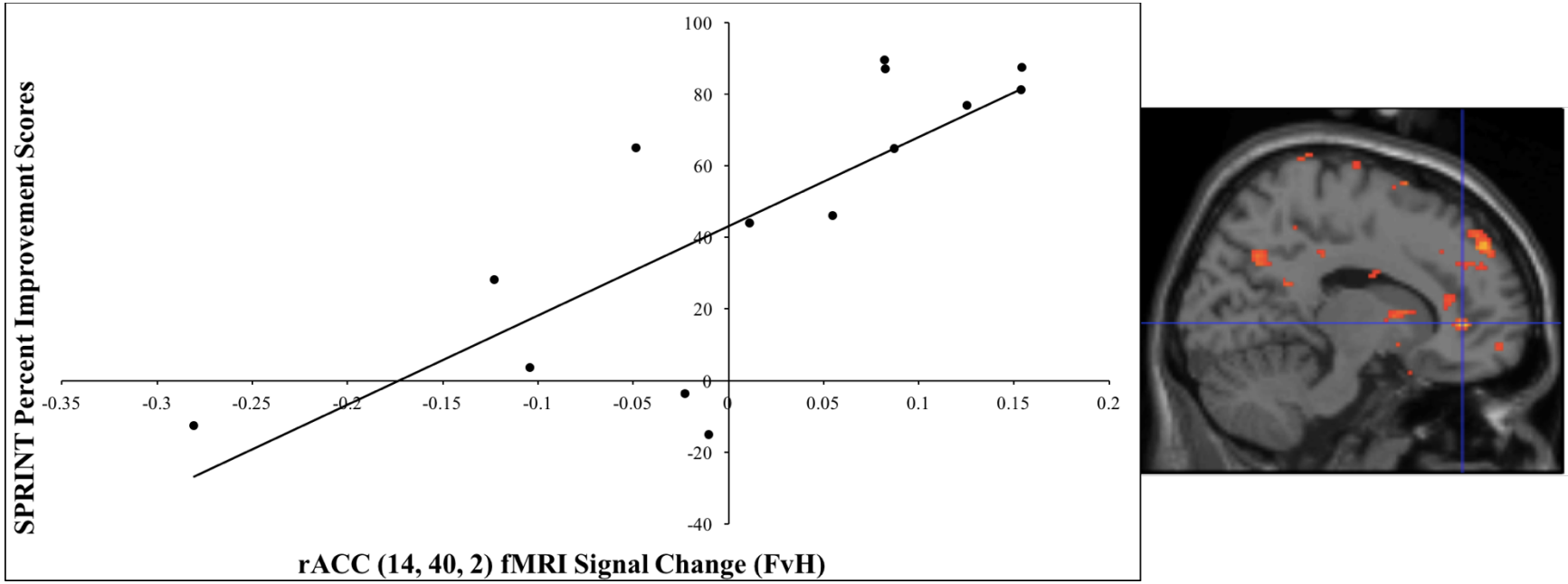

Figure 3. Correlation between pre-treatment activation seen in the rostral anterior cingulate cortex (rACC; MNI coordinates, 14, 40, 2; $z = 3.67$, $p = .000$) during the viewing of fearful versus happy (FvH) facial expressions and symptom severity improvement as measured by the Short Posttraumatic Stress Disorder (PTSD) Rated Interview (SPRINT) percent improvement scores.

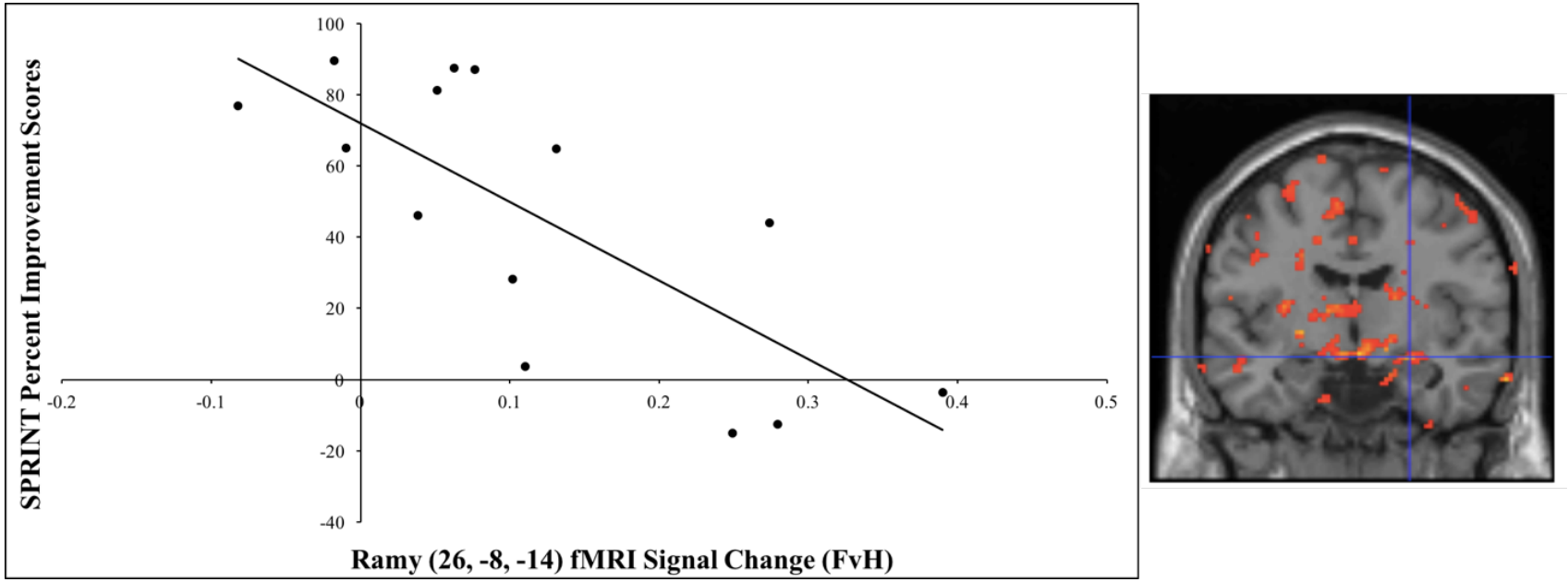

Figure 4. Correlation between pre-treatment activation seen in the right amygdala (Ramy; MNI coordinates, 26, -8, -14; $z = 3.43$, $p = .000$) during the viewing of fearful versus happy (FvH) facial expressions and symptom severity improvement as measured by the Short Posttraumatic Stress Disorder (PTSD) Rated Interview (SPRINT) percent improvement scores.

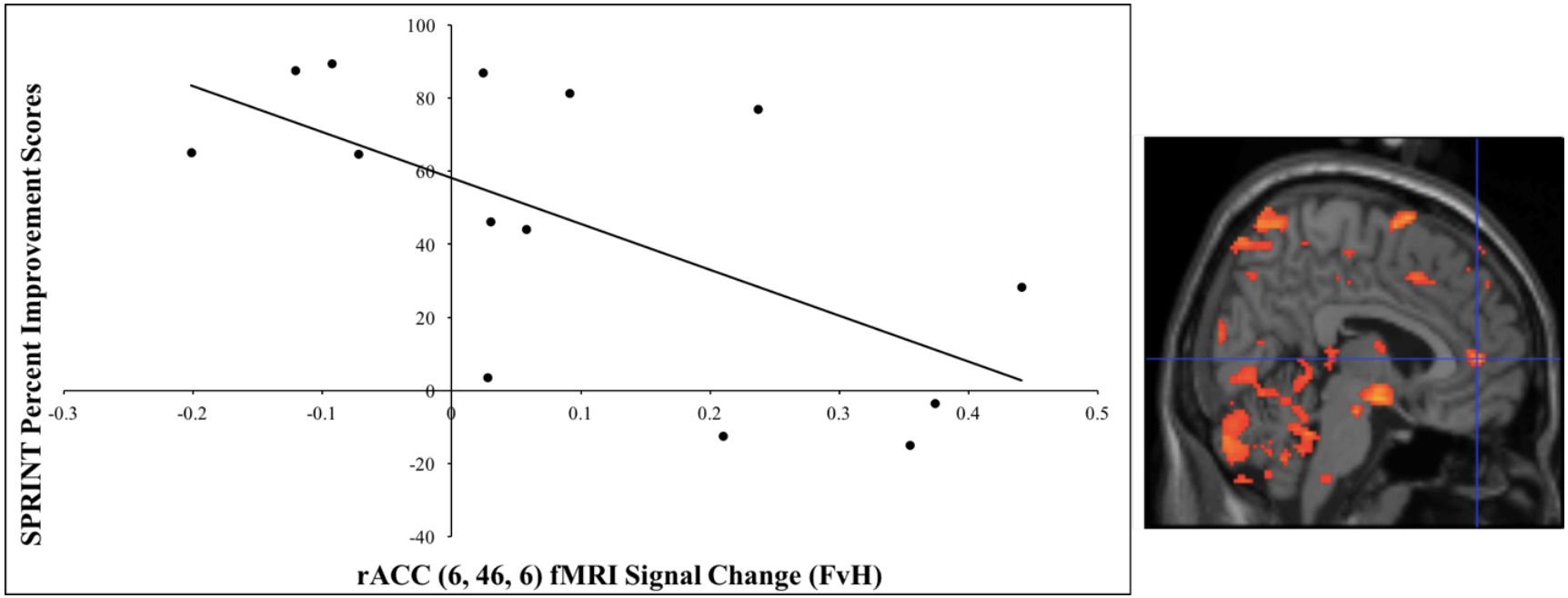

Figure 5. Correlation between pre-treatment activation seen in the rostral anterior cingulate cortex (rACC; MNI coordinates, 6, 46, 6; $z = 3.18$, $p = .000$) during the viewing of fearful versus happy (FvH) facial expressions and symptom severity improvement as measured by the Short Posttraumatic Stress Disorder (PTSD) Rated Interview (SPRINT) percent improvement scores.